HHS Public Access

Author manuscript

Int J Cancer. Author manuscript; available in PMC 2017 March 01.

Published in final edited form as:

Int J Cancer. 2016 March 1; 138(5): 1085–1093. doi:10.1002/ijc.29857.

FETAL GROWTH AND SUBSEQUENT MATERNAL RISK OF THYROID CANCER

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Abstract

Thyroid cancer has peak incidence among women of reproductive age, and growth factors, which have procarcinogenic properties, may play an important etiologic role. However, the association between fetal growth rate during a woman's pregnancy and her subsequent risk of thyroid cancer has not been previously examined. We conducted a national cohort study of 1,837,634 mothers who had a total of 3,588,497 live-births in Sweden in 1973-2008, followed up for thyroid cancer incidence through 2009. There were 2,202 mothers subsequently diagnosed with thyroid cancer in 36.8 million person-years of follow-up. After adjusting for maternal age, height, weight, smoking, and sociodemographic factors, high fetal growth (birth weight standardized for gestational age and sex) was associated with a subsequent increased risk of thyroid cancer in the mother (incidence rate ratio [IRR] per additional 1 standard deviation, 1.05; 95% CI, 1.01-1.09; P=0.02). Each 1,000 g increase in the infant's birth weight was associated with a 13% increase in the mother's subsequent risk of thyroid cancer (IRR, 1.13; 95% CI, 1.05-1.22; P=0.001). These findings appeared to involve both papillary and follicular subtypes, and did not vary significantly by the mother's height, weight, or smoking status. In this large national cohort study, high fetal growth during a woman's pregnancy was independently associated with a subsequent increased risk of her

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Article category: Research Article (Epidemiology)

Novelty and impact: In this large national cohort study, high fetal growth during a woman's pregnancy was independently associated with a subsequent increased risk of her developing thyroid cancer. These findings suggest an important role of maternal growth factors in the development of thyroid cancer, and potentially may help facilitate the identification of high-risk subgroups of women.

There were no conflicts of interest.

FUNDING

Author Contributions: Dr. Jan Sundquist had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Crump, J. Sundquist, Sieh, Winkleby, K. Sundquist.

Acquisition of data: J. Sundquist, K. Sundquist.

Analysis and interpretation of data: Crump, J. Sundquist, Sieh, Winkleby, K. Sundquist.

Drafting of the manuscript: Crump.

Critical revision of the manuscript for important intellectual content: Crump, J. Sundquist, Sieh, Winkleby, K. Sundquist.

Statistical analysis: Crump, J. Sundquist.

Obtained funding: Crump, J. Sundquist, K. Sundquist.

developing thyroid cancer. If confirmed, these findings suggest an important role of maternal growth factors in the development of thyroid cancer, and potentially may help facilitate the identification of high-risk subgroups of women.

Keywords

fetal development; mothers; pregnancy; risk factors; thyroid neoplasms

INTRODUCTION

Thyroid cancer affects women ~3 times more commonly than men, and its incidence among women peaks in the later reproductive years.[1] The worldwide incidence of thyroid cancer has steadily increased over the past three decades, especially among women, and this increase appears only partly due to improved detection.[2] In most countries, known risk factors such as ionizing radiation and genetic syndromes account for a minority of cases,[3] which has prompted investigations of other factors that potentially could facilitate the identification of high-risk subgroups. A number of studies have reported that increased height or body mass index (BMI) in either childhood[4] or adulthood[5-10] is associated with a modestly increased risk of adult thyroid cancer, possibly related to growth factor pathways involving insulin-like growth factor I (IGF-I).[11, 12] IGF-I is known to have pro-carcinogenic properties and to be produced locally in thyroid cancer cells.[11, 12] Because IGF-1 levels are also positively correlated with fetal growth,[13-15] we hypothesize that high fetal growth during a woman's pregnancy is independently associated with a subsequent increased risk of her developing thyroid cancer. To our knowledge, this hypothesis has not been previously examined. If such an association is found, this information would provide additional insights into etiologic pathways for thyroid cancer and may help identify subgroups of women at high risk of this disease.

We conducted a national cohort study to examine fetal growth (birth weight standardized for gestational age and sex) and other gestational factors in relation to the risk of thyroid cancer and its most common subtypes among all ~1.8 million women who gave birth during 1973-2008 in Sweden. Detailed information on gestational factors and thyroid cancer incidence were obtained from birth and cancer registries that are nearly 100% complete nationwide. Our aims were to examine whether high fetal growth and other gestational factors in the offspring are associated with subsequent increased risk of thyroid cancer and its most common subtypes in a large national cohort of mothers.

MATERIALS AND METHODS

Study Population

We identified 3,595,055 live-births among 1,840,473 mothers in the Swedish Birth Registry from 1973 through 2008. We excluded all 1,251 (0.03%) births that occurred after a prior diagnosis of thyroid cancer in the mother. To remove possible coding errors, we excluded 5,307 (0.1%) others that had a reported birth weight more than four standard deviations (SD) above or below the mean birth weight for gestational age and sex based on a Swedish

reference growth curve.[16] A total of 3,588,497 births among 1,837,634 mothers (99.8% of the original cohort) remained for inclusion in the study. This study was approved by the Regional Ethics Committee of Lund University in Sweden.

Ascertainment of Thyroid Cancer

The study cohort was followed up for thyroid cancer incidence from the time of first delivery through December 31, 2009. All incident thyroid cancer cases were identified using International Classification of Diseases, Version 7 (*ICD-7*) code 194 in the Swedish Cancer Registry, and histologic subtypes were classified according to standard WHO codes.[17] The Swedish Cancer Registry includes all primary incident cancers in Sweden since 1958, with compulsory reporting nationwide.

Ascertainment of Gestational Factors

Gestational and maternal characteristics that are potentially associated with thyroid cancer were identified from the Swedish Birth Registry and national census data, which were linked using an anonymous personal identification number. The following variables were examined as adjustment variables or predictors of interest: date of delivery (included to adjust for follow-up time, and modeled simultaneously as a continuous variable and categorical variable by decade to allow for a non-linear effect); fetal growth of the offspring (a standardized fetal growth variable defined as the number of SD from the mean birth weight for gestational age and sex based on a Swedish reference growth curve,[16] modeled alternatively as a categorical [<−1; −1 to <1; ≥1 SD] or continuous variable); gestational age at birth of the offspring (based primarily on maternal report of last menstrual period in the 1970s, at which time ultrasound estimation was gradually introduced until it was used exclusively starting in the 1990s; modeled alternatively as a categorical [<34, 34-36, 37-41, ≥42 weeks] or continuous variable); multiple gestation (singleton vs. twin or higher order); maternal age at delivery (<25, 25-29, 30-34, ≥35 years); maternal parity (1, 2, 3, ≥4); maternal height, modeled alternatively as a categorical (<160.0, 160.0-172.9, ≥173.0 cm) or continuous variable, included because taller women deliver larger babies on average[18] (correlation between maternal height and fetal growth in the present cohort = 0.21; $P<0.0001$), and may have increased risk of thyroid cancer[5]; maternal pre-pregnancy weight, modeled alternatively as a categorical (<60.0, 60.0-69.9, ≥70.0 kg) or continuous variable, included because obese women deliver larger babies on average[19] (correlation between maternal weight or BMI and fetal growth in the present cohort = 0.29 and 0.22, respectively; $P<0.0001$ for both), and may have increased risk of thyroid cancer[7-10]; maternal smoking (0, 1-9, ≥10 cigarettes/day), ascertained at the beginning of prenatal care and included because maternal smoking is associated with lower birthweight[20] and lower risk of thyroid cancer[21, 22]; maternal education level (compulsory high school or less [≤9 years], practical high school or some theoretical high school [10-11 years], theoretical high school and/or some college [12-14 years], college and/or post-graduate study [≥15 years]); maternal marital status (married/cohabiting, never married, widowed/divorced); and maternal country of birth (Sweden, other Western countries [Europe, US, Canada, Australia, New Zealand], non-Western countries).

In addition, we examined maternal history of gestational or pre-existing diabetes mellitus as a potential confounder, because it has been associated with delivering a high birth weight infant[23] and increased risk of thyroid cancer.[24] Diabetes mellitus was identified by any inpatient or outpatient diagnosis prior to delivery using both the Swedish Hospital Registry, which includes all inpatient diagnoses from the six most populous counties of southern Sweden since 1964 and nationwide since 1987, and the Swedish Outpatient Registry, which includes outpatient diagnoses nationwide since 2001. However, there were too few mothers diagnosed with diabetes who subsequently developed thyroid cancer (n=15) to obtain meaningful risk estimates, and adjustment for diabetes made no difference in other risk estimates, hence it was not included in further analyses.

As alternatives to the standardized fetal growth variable, we also examined birth weight (modeled alternatively as a categorical [<2500, 2500-3999, ≥4000 g] or continuous variable) and birth length (crown-heel length in cm, modeled alternatively as a categorical [<48, 48-52, ≥53 cm] or continuous variable) in separate models. As an alternative to maternal height and weight, we also examined BMI (modeled alternatively as a categorical [<18.5, 18.5-24.9, 25.0-29.9, ≥30.0] or continuous variable) in a separate model.

Missing data for each variable were imputed using a standard multiple imputation procedure based on the variable's relationship with all other covariates.[25, 26] Missing data were infrequent for the standardized fetal growth variable (0.5%), birth weight (0.3%), birth length (1.1%), gestational age at birth (0.2%), maternal age (0.1%), parity (5.9%), and maternal education (4.1%). Maternal height, weight, and smoking data were available only starting in 1982, and therefore were missing for 36.5%, 42.5%, and 30.4% of pregnancies, respectively. As an alternative to multiple imputation, a sensitivity analysis was performed after excluding births for which any of these data were missing. Data were complete for all other variables.

Statistical Analysis

Poisson regression with robust standard errors was used to estimate incidence rate ratios (IRRs) and 95% confidence intervals (CIs) for associations between gestational or maternal factors and subsequent maternal risk of thyroid cancer.[27] Clustering of births by mother was used to account for correlation among siblings while allowing information from each birth to contribute to the risk estimates. Sensitivity analyses also were performed after restricting alternatively to each mother's first or last birth. All models were adjusted for date of delivery (to account for follow-up time), maternal age, height, weight, smoking, and other variables that were found to be associated with thyroid cancer (parity, marital status, and maternal country of birth). Poisson model goodness-of-fit was assessed using deviance and Pearson chi-squared tests, which indicated a good fit in all models.

Multinomial logistic regression was used to test for heterogeneity in the association between fetal growth and the mother's risk of thyroid cancer by age at diagnosis (comparing <50 to ≥50 years), time since delivery (comparing <5 to ≥5 years), and subtype (comparing papillary to follicular thyroid cancer). Likelihood ratio tests were used to assess for interaction between fetal growth and maternal height, weight, or smoking in relation to the

maternal risk of thyroid cancer or its major subtypes. All statistical tests were 2-sided and used an α-level of 0.05. All analyses were conducted using Stata version 13.0.[26]

RESULTS

Among the 1,837,634 mothers in this cohort, 2,202 (0.12%) were subsequently diagnosed with thyroid cancer in 36.8 million person-years of follow-up. There were 668 (30.3%) cases with unavailable subtype information. Of the remaining 1,534 cases, the most common subtypes were papillary (n=1,194; 77.8%) and follicular (n=291; 19.0%). The median age of all women at the end of follow-up was 47.6 years (mean 48.0, SD 11.6, range 14.5 to 78.5). The median age at diagnosis was 41.3 years for any thyroid cancer (mean 42.1, SD 10.2, range 18.0 to 75.5), 44.1 years for papillary subtype (mean 44.4, SD 10.2, range 18.0 to 75.5), and 46.0 years for follicular subtype (mean 45.7, SD 9.8, range 18.4 to 68.7).

Thyroid Cancers Overall

High fetal growth in the offspring was independently associated with a subsequent increased risk of thyroid cancer in the mother (adjusted IRR for fetal growth ≥1 vs. −1 to <1 SD, 1.13; 95% CI, 1.02-1.24; P=0.02), including a significant linear trend across the full range of fetal growth (adjusted IRR per additional 1 SD of fetal growth, 1.05; 95% CI, 1.01-1.09, P=0.02) (Table 1). A similar positive trend was found in the mother's risk of thyroid cancer by her offspring's birth weight or birth length when examined as alternatives to the standardized fetal growth variable (Table 1). Each 1,000 g increase in the offspring's birth weight was associated with a 13% increase in the mother's subsequent risk of thyroid cancer (adjusted IRR, 1.13; 95% CI, 1.05-1.22, P=0.001). A slight positive trend was also found in the mother's risk of thyroid cancer by higher gestational age at birth of her offspring (adjusted IRR per additional 1 week, 1.03; 95% CI, 1.01-1.05, P=0.01). With the exception of the date of delivery variable (which accounted for follow-up time), adjustment for any combination of other covariates had minimal effect on any of the risk estimates.

Maternal height (but not weight or BMI) was also positively associated with an increased risk of thyroid cancer (adjusted IRR per additional 5 cm in height, 1.15; 95% CI, 1.10-1.22; P<0.001). Other maternal risk factors for thyroid cancer included maternal birth outside of Sweden, especially in non-Western countries (adjusted IRR relative to Sweden, 1.83; 95% CI, 1.55-2.16; P<0.001), and highest parity (adjusted IRR for parity ≥4 vs. 1, 1.22; 95% CI, 1.03-1.44; P=0.02). Maternal smoking was associated with a slightly reduced risk of thyroid cancer (P_{trend}=0.03; Table 1). Mothers who had never married also had a lower risk compared with married women (adjusted IRR, 0.85; 95% CI, 0.75-0.96; P=0.007). Sex of the child, multiple birth, maternal age, and maternal education level were not associated with maternal risk of thyroid cancer (Table 1).

The association between high fetal growth and subsequent maternal risk of thyroid cancer appeared slightly stronger among women diagnosed at age <50 years (adjusted odds ratio [OR] per additional 1 SD, 1.06; 95% CI, 1.02-1.11; P=0.006; based on 1,685 thyroid cancer cases) than those diagnosed at age ≥50 years (adjusted OR per additional 1 SD, 1.03; 95% CI, 0.95-1.11; P=0.53; based on 517 cases), although the difference between these risk estimates was non-significant ($P_{heterogeneity}$=0.43; data not shown in the table). This

association also appeared similar among those diagnosed ≥5 years after delivery (adjusted OR per additional 1 SD, 1.05; 95% CI, 1.01-1.10; P=0.02; based on 1,766 cases) compared with those diagnosed <5 years after delivery (adjusted OR per additional 1 SD, 1.07; 95% CI, 1.00-1.15; P=0.05; based on 436 cases) ($P_{heterogeneity}$=0.64; data not shown in the table).

Sensitivity analyses that were restricted alternatively to each mother's first or last birth produced very similar results as the main analysis, including nearly identical risk estimates for fetal growth (adjusted IRRs per additional 1 SD, first births: 1.05; 95% CI, 1.01-1.09; P=0.02; last births: 1.06; 95% CI, 1.01-1.11; P=0.009) ($P_{heterogeneity}$=0.94; data not shown in the table). A sensitivity analysis that excluded births with missing data for maternal height, weight, or smoking also yielded the same point estimate for fetal growth as the main analysis (adjusted IRR per additional 1 SD, 1.05; 95% CI, 0.99-1.11; P=0.13). There was no evidence of interaction between fetal growth and maternal height (P=0.23), weight (P=0.46), or smoking (P=0.31) in relation to the maternal risk of thyroid cancer.

Thyroid Cancer Subtypes

Subtype-specific analyses had limited statistical power for detecting significant associations. However, fetal growth, birth weight, and birth length in the offspring, and maternal height and non-Swedish birth, appeared positively associated with both papillary and follicular subtypes as for thyroid cancers overall. Specifically, the association between fetal growth in the offspring and maternal risk of papillary subtype had the same IRR point estimate (adjusted IRR per additional 1 SD, 1.05; 95% CI, 1.00-1.11; P=0.06) compared with thyroid cancers overall (Table 1). The association with follicular subtype had a slightly lower point estimate (adjusted IRR per additional 1 SD, 1.03; 95% CI, 0.93-1.14; P=0.60), but this was non-significantly different compared with that for papillary subtype ($P_{heterogeneity}$=0.69). High birth weight of the offspring appeared to be associated with higher maternal risk of both subtypes, especially follicular. Each 1,000 g increase in the offspring's birth weight was associated with a 25% increase in the mother's subsequent risk of follicular thyroid cancer (adjusted IRR, 1.25; 95% CI, 1.04-1.51, P=0.02).

Maternal height (but not weight or BMI) and maternal birth outside of Sweden also were positively associated with higher risk of both papillary and follicular subtypes (Table 1). Other subtype-specific risk factors included high gestational age at birth of the offspring, which was associated with increased maternal risk of follicular (P_{trend}=0.003) but not papillary (P_{trend}=0.35) subtype (Table 1). Highest parity was associated with increased risk of papillary (but not follicular) subtype (adjusted IRR for parity ≥4 vs. 1, 1.33; 1.08-1.64; P=0.006). Maternal smoking was associated with lower risk of follicular (P_{trend}=0.04) but not papillary (P_{trend}=0.29) subtype. Sex of the child, multiple gestation, maternal age, education level, and marital status were not clearly associated with either subtype (Table 1). There also was no evidence of interaction between fetal growth and maternal height, weight, or smoking in relation to maternal risk of either papillary or follicular subtype (P>0.05 for each).

DISCUSSION

In this large national cohort study, we found that high fetal growth during a woman's pregnancy was associated with a subsequent increased risk of her developing thyroid cancer, independently of her height, weight, smoking status, and sociodemographic factors. This finding appeared to involve both papillary and follicular subtypes, although power was limited for subtype analyses. If confirmed, these findings identify high fetal growth during a woman's pregnancy as a new independent risk factor for thyroid cancer.

These findings contribute to other evidence suggesting a link between high birth weight in the offspring and increased cancer risk in the mother, including an association with breast cancer reported in several[28-30] though not all[31, 32] studies. However, to our knowledge, no studies have examined fetal growth in relation to maternal risk of thyroid cancer. The findings we observed are biologically plausible because of the known effects of growth factors on fetal growth and carcinogenesis.[33-35] Fetal growth is positively correlated with umbilical cord levels of IGF-I[13, 14] and with the rate of increase in maternal IGF-I levels in mid-pregnancy.[15] IGF-I levels vary considerably in the general population and are known to have pro-carcinogenic properties including inhibition of cellular apoptosis.[36] The IGF-I receptor (IGF-I R) is overexpressed and IGF-I is locally produced in thyroid cancer cells,[11, 12] and immunoreactivity for IGF-I and IGF-1 R is positively correlated with thyroid tumor diameter.[37] High IGF-I levels in adulthood have been associated with increased risk of thyroid cancer[38] as well as cancers of other sites including the breast[39] and colon.[40] Our findings provide further evidence suggesting a role of maternal growth factors in the development of thyroid cancer.

We also found that maternal height was positively associated with higher risk of thyroid cancer overall and both papillary and follicular subtypes. This finding is consistent with previous studies reporting that taller children[4] or adults[5] have a modestly increased risk of thyroid cancer in adulthood. However, we found no association between adult weight or BMI and risk of thyroid cancer, consistent with a previous study of Swedish men,[41] but in contrast to a number of studies in other populations.[7-10] A recent cohort study reported that the risk of thyroid cancer was highest among women whose body shape increased from lean at menarche to obese in adulthood.[8] Additional studies with longitudinal measurements of height and weight throughout early life are needed to clarify the relative influences of these factors on the risk of thyroid cancer in adulthood.

Highest parity (≥4) was modestly associated with papillary but not follicular thyroid cancer in this cohort. An association between high parity and thyroid cancer has been reported in some[42-44] but not all[45, 46] previous studies. A potential mechanism may involve high cumulative estrogen exposures during pregnancy. Estrogen is a potent growth factor for thyroid cancer cells,[47] and there is evidence for abnormal estrogen metabolism in thyroid cancer[48] and for estrogen induction of metastatic potential in papillary thyroid cancer cells.[49] We also found that post-term delivery (≥42 weeks) was associated with increased maternal risk of follicular (but not papillary) thyroid cancer, which potentially could be related to prolonged gestational exposures to estrogens or growth factors. However, to our

knowledge this finding has not been previously reported and therefore will need confirmation in other studies.

The relatively higher risk of thyroid cancer we found among mothers born outside of Sweden is consistent with previously reported higher incidence rates in most of Europe, the Americas, and Asia compared with Sweden.[50] Sweden is one of the few countries that reported a decline in thyroid cancer incidence over the past three decades,[50] which is not well explained but seems unlikely related to diagnostic differences given the long-standing universal health care access in Sweden.

Important strengths of this study include its large population-based cohort design. Linkage of birth and cancer registries provided detailed information on gestational factors and thyroid cancer incidence that was nearly 100% complete nationwide.[51, 52] The study cohort consisted of all women of reproductive ages, who are a key population of interest because they are more susceptible to thyroid cancer than other demographic groups. A national cohort design prevented selection bias that may potentially occur in case-control studies, and the use of registry data with prospectively ascertained birth characteristics, maternal height and weight, and thyroid cancer incidence prevented bias that may result from self-reporting. We were able to examine the specific components of birth weight—fetal growth and gestational age—while adjusting for maternal height, weight, smoking, and other potential confounders.

Limitations include a lack of information on radiation exposures, which are a known important risk factor for thyroid cancer.[53] Though we adjusted for maternal smoking and other potential confounders that are unavailable in most large population-based studies, residual confounding is possible. We also adjusted for maternal height and weight, although longitudinal measurements were unavailable for examining the influence of body size changes over time. In addition, Sweden has among the lowest incidences of thyroid cancer worldwide, which may reflect important differences in unmeasured exposures. Our findings warrant further investigation to determine their effect size in populations in which thyroid cancer is more common.

In summary, this large population-based cohort study is the first study to examine fetal growth in relation to the subsequent maternal risk of thyroid cancer. We found that high fetal growth during a woman’s pregnancy was independently associated with a higher risk of her subsequently developing thyroid cancer, irrespective of her own height, weight, or smoking status. If confirmed, these findings suggest an important role of maternal growth factors such as IGF-I in the development of thyroid cancer. Further elucidation of the underlying pathways will improve our understanding of disease etiology and potentially facilitate the identification of high-risk subgroups of women.

ACKNOWLEDGMENTS

This work was supported by the National Cancer Institute at the National Institutes of Health (R03 CA171017); the Swedish Research Council; and ALF project grant, Region Skåne/Lund University, Sweden. The funding agencies had no role in the design and conduct of the study; in the collection, analysis, and interpretation of the data; or in the preparation, review, or approval of the manuscript.

Abbreviations

BMI	(body mass index)
ICD	(International Classification of Diseases)
IGF-I	(insulin-like growth factor I)
IGF-I R	(insulin-like growth factor I receptor)
IRR	(incidence rate ratio)
OR	(odds ratio)
SD	(standard deviation)
WHO	(World Health Organization)

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Table 1

Adjusted incidence rate ratios for associations between gestational factors and subsequent maternal risk of thyroid cancer (1973-2009)[a]

	No Thyroid Cancer	Any Thyroid Cancer				Papillary Thyroid Cancer				Follicular Thyroid Cancer			
	N=3,584,464 births to 1,835,432 mothers	N=4,033 births to 2,202 mothers	IRR	95% CI	*P*	N=2,339 births to 1,194 mothers	IRR	95% CI	*P*	N=551 births to 292 mothers	IRR	95% CI	*P*
Offspring variables													
Sex													
Male	1,842,315 (51.4)	2,049 (50.8)	1.00			1,192 (51.0)	1.00			265 (48.1)	1.00		
Female	1,742,149 (48.6)	1,984 (49.2)	1.03	0.96, 1.09	0.45	1,147 (49.0)	1.02	0.94, 1.11	0.68	286 (51.9)	1.14	0.95, 1.37	0.15
Fetal growth (SD)													
<−1	527,966 (14.7)	594 (14.7)	0.95	0.86, 1.05	0.32	407 (17.4)	0.98	0.86, 1.12	0.74	76 (13.8)	0.93	0.69, 1.24	0.60
−1 to 1	2,524,987 (70.4)	2,783 (69.0)	1.00			1,523 (65.1)	1.00			389 (70.6)	1.00		
≥1	531,511 (14.8)	656 (16.3)	1.13	1.02, 1.24	0.02	409 (17.5)	1.13	0.99, 1.29	0.08	86 (15.6)	1.02	0.78, 1.33	0.90
Per SD (trend test)			1.05	1.01, 1.09	0.02		1.05	1.00, 1.11	0.06		1.03	0.93, 1.14	0.60
Birth weight (g)													
<2500	151,465 (4.2)	141 (3.5)	0.87	0.72, 1.05	0.14	89 (3.8)	0.92	0.72, 1.17	0.49	13 (2.4)	0.60	0.31, 1.13	0.11
2500-3999	2,789,853 (77.8)	3,103 (76.9)	1.00			1,790 (76.7)	1.00			425 (77.1)	1.00		
≥4000	643,146 (17.9)	789 (19.6)	1.11	1.01, 1.22	0.04	454 (19.5)	1.08	0.95, 1.23	0.21	113 (20.5)	1.13	0.87, 1.46	0.37
Per 1000 g (trend test)			1.13	1.05, 1.22	0.001		1.11	1.00, 1.22	0.05		1.25	1.04, 1.51	0.02
Birth length (cm)													
<48	382,232 (10.7)	359 (8.9)	0.87	0.77, 0.99	0.03	225 (9.6)	0.92	0.78, 1.08	0.30	36 (6.5)	0.63	0.43, 0.92	0.02
48-52	2,623,178 (73.2)	2,931 (72.7)	1.00			1,692(72.3)	1.00			414 (75.1)	1.00		
≥53	579,054 (16.1)	743 (18.4)	1.13	1.03, 1.24	0.01	422 (18.0)	1.12	0.99, 1.26	0.08	101 (18.3)	1.07	0.83, 1.39	0.60
Per cm (trend test)			1.03	1.01, 1.05	<0.001		1.02	1.00, 1.04	0.10		1.06	1.01, 1.10	0.009
Gestational age at birth (weeks)													
<34	54,789 (1.5)	53 (1.3)	0.94	0.69, 1.28	0.69	39 (1.7)	1.13	0.78, 1.63	0.52	2 (0.4)	0.27	0.07, 1.06	0.06
34-36	154,502 (4.3)	151 (3.7)	0.90	0.75, 1.08	0.24	85 (3.6)	0.85	0.67, 1.09	0.19	22 (4.0)	0.98	0.61, 1.58	0.95
37-41	3,076,364 (85.8)	3,419 (84.8)	1.00			1,998 (85.4)	1.00			458 (83.1)	1.00		

	No Thyroid Cancer	Any Thyroid Cancer				Papillary Thyroid Cancer				Follicular Thyroid Cancer			
	N=3,584,464 births to 1,835,432 mothers	N=4,033 births to 2,202 mothers	IRR	95% CI	*P*	N=2,339 births to 1,194 mothers	IRR	95% CI	*P*	N=551 births to 292 mothers	IRR	95% CI	*P*
≥42	298,809 (8.3)	410 (10.2)	1.11	0.99, 1.24	0.08	217 (9.3)	1.08	0.92, 1.26	0.34	69 (12.5)	1.46	1.10, 1.93	0.008
Per week (trend test)			1.03	1.01, 1.05	0.01		1.01	0.99, 1.04	0.35		1.10	1.03, 1.17	0.003
Multiple gestation													
Singleton	3,499,206 (97.6)	3,953 (98.0)	1.00			2,276 (97.3)	1.00			548 (99.5)	1.00		
Twin or higher order	85,258 (2.4)	80 (2.0)	0.90	0.66, 1.22	0.49	63 (2.7)	1.13	0.80, 1.61	0.49	3 (0.5)	0.24	0.06, 1.04	0.06
Maternal variables													
Age (years)													
<25	765,976 (21.4)	890 (22.1)	0.90	0.82, 0.98	0.02	515 (22.0)	0.98	0.87, 1.11	0.75	108 (19.6)	0.79	0.61, 1.02	0.07
25-29	1,259,532 (35.1)	1,513 (37.5)	1.00			845 (36.1)	1.00			217 (39.4)	1.00		
30-34	1,038,155 (29.0)	1,081 (26.8)	0.97	0.89, 1.05	0.48	642 (27.5)	0.97	0.87, 1.08	0.53	150 (27.2)	0.92	0.74, 1.14	0.45
≥35	520,801 (14.5)	549 (13.6)	1.04	0.92, 1.17	0.55	337 (14.4)	1.01	0.86, 1.18	0.95	76 (13.8)	0.97	0.70, 1.36	0.88
Per higher category (trend test)				0.99, 1.09				0.94, 1.07				0.92, 1.20	
Parity													
1	1,505,961 (42.0)	1,599 (39.6)	1.00			929 (39.7)	1.00			224 (40.8)	1.00		
2	1,304,657 (36.4)	1,452 (36.0)	1.00	0.95, 1.05	0.92	831 (35.5)	1.02	0.96, 1.08	0.47	194 (35.3)	0.93	0.82, 1.06	0.27
3	543,315 (15.2)	661 (16.4)	1.08	0.98, 1.18	0.13	378 (16.2)	1.10	0.97, 1.24	0.13	94 (17.0)	1.05	0.82, 1.36	0.70
≥4	230,531 (6.4)	2321 (8.0)	1.22	1.03, 1.44	0.02	201 (8.6)	1.33	1.08, 1.64	0.006	39 (6.9)	1.00	0.62, 1.63	0.99
Per higher category (trend test)			1.05	1.01, 1.10	0.03		1.08	1.02, 1.14	0.01		1.01	0.88, 1.15	0.89
Height (cm)													
<160.0 (5 ft. 3 in.)	295,645 (8.3)	233 (5.8)	0.87	0.73, 1.05	0.15	168 (7.2)	0.89	0.71, 1.11	0.29	37 (6.7)	0.95	0.59, 1.54	0.83
160.0-172.9	2,935,842 (81.9)	3,445 (85.4)	1.00			1,903 (81.4)	1.00			462 (83.9)	1.00		
≥173.0 (5 ft. 8 in.)	352,977 (9.8)	355 (8.8)	1.32	1.13, 1.56	0.001	268 (12.5)	1.45	1.20, 1.75	<0.001	52 (9.4)	1.21	0.79, 1.88	0.38
Per 5 cm (trend test)			1.15	1.10, 1.22	<0.001		1.16	1.08, 1.23	<0.001		1.17	1.03, 1.34	0.02
Weight (kg)													
<60.0 (132 lbs.)	871,279 (24.3)	851 (21.1)	0.99	0.90, 1.09	0.86	541 (23.1)	1.01	0.89, 1.15	0.83	124 (22.5)	1.04	0.81, 1.34	0.76
60.0-69.9	2,037,350 (56.8)	2,586 (64.1)	1.00			1,381 (59.0)	1.00			336 (61.0)	1.00		

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≥70.0 (154 lbs.)	675,835 (18.9)	596 (14.8)	1.12	0.99, 1.25	0.06	417 (17.8)	1.10	0.95,1.27	0.21	91 (16.5)	1.17	0.85, 1.60	0.33
Per 5 kg (trend test)			1.02	0.99, 1.04	0.23		1.01	0.98, 1.04	0.53		0.98	0.92, 1.05	0.63
Body mass index													
<18.5	83,274 (2.3)	68 (1.7)	0.81	0.62, 1.07	0.14	46 (2.0)	0.84	0.60, 1.19	0.33	13 (2.4)	1.09	0.60, 1.97	0.77
18.5-25	2,893,954 (80.7)	3,489 (86.5)	1.00			1,964 (84.0)	1.00			470 (85.3)	1.00		
25-30	459,581 (12.8)	393 (9.7)	1.04	0.92, 1.18	0.51	263 (11.2)	1.00	0.85, 1.16	0.96	56 (10.2)	1.00	0.71, 1.39	0.98
>30	147,655 (4.1)	83 (2.1)	0.89	0.69, 1.16	0.41	66 (2.8)	0.90	0.67, 1.21	0.49	12 (2.2)	0.83	0.41, 1.68	0.60
Per 1 unit higher (trend test)			1.00	0.99, 1.02	0.84		1.00	0.98, 1.02	0.88		0.98	0.94, 1.02	0.33
Smoking (cigarettes/day)													
0	2,950,003 (82.3)	3,367 (83.5)	1.00			1,926 (82.3)	1.00			475 (86.2)	1.00		
1-9	467,891 (13.1)	514 (12.7)	0.89	0.79, 0.99	0.04	306 (13.1)	0.92	0.79, 1.07	0.30	56 (10.2)	0.68	0.48, 0.96	0.03
≥10	166,570 (4.6)	152 (3.8)	0.84	0.68, 1.04	0.12	107 (4.6)	0.91	0.69, 1.19	0.48	20 (3.6)	0.71	0.41, 1.21	0.21
Per higher category (trend test)			0.90	0.83, 0.99	0.03		0.94	0.84, 1.05	0.29		0.77	0.60, 0.99	0.04
Education (years)													
≤9	707,162 (19.7)	1,024 (25.4)	1.00			524 (22.4)	1.00			149 (27.0)	1.00		
10-11	1,203,828 (33.6)	1,392 (34.5)	0.88	0.78, 1.00	0.06	821 (35.1)	0.97	0.82, 1.16	0.78	190 (34.5)	0.73	0.52, 1.04	0.08
12-14	1,093,362 (30.5)	1,045 (25.9)	0.91	0.79, 1.05	0.21	652 (27.9)	0.99	0.82, 1.21	0.96	132 (24.0)	0.64	0.42, 0.96	0.03
≥15	580,112 (16.2)	572 (14.2)	0.98	0.83, 1.16	0.80	342 (14.6)	1.06	0.85, 1.34	0.59	80 (14.5)	0.76	0.49, 1.18	0.23
Per higher category (trend test)			0.99	0.94, 1.05	0.72		1.02	0.95, 1.10	0.62		0.89	0.76, 1.04	0.14
Marital status													
Married/cohabiting	2,878,913 (80.3)	3,097 (76.8)	1.00			1,833 (78.3)	1.00			435 (79.0)	1.00		
Never married	351,846 (9.8)	490 (12.1)	0.85	0.75, 0.96	0.007	238 (10.2)	0.89	0.75, 1.05	0.16	58 (10.5)	0.86	0.60, 1.23	0.42
Divorced/widowed	353,705 (9.9)	446 (11.1)	1.09	0.97, 1.22	0.14	268 (11.5)	1.16	1.00, 1.34	0.05	58 (10.5)	1.11	0.83, 1.48	0.50
Country of birth													
Sweden	2,865,394 (79.9)	3,081 (76.4)	1.00			1,743 (74.5)	1.00			417 (75.7)	1.00		

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Other Western countries	419,468 (11.7)	576 (14.3)	1.22	1.07, 1.40	0.003	324 (13.9)	1.25	1.04, 1.49	0.02	88 (16.0)	1.41	1.00, 1.98	0.05
Other non-Western countries	301,296 (8.4)	376 (9.3)	1.83	1.55, 2.16	<0.001	272 (11.6)	1.91	1.56, 2.35	<0.001	46 (8.3)	1.44	0.89, 2.33	0.14

IRR = incidence rate ratio.

[a]All risk estimates are adjusted for maternal age, date of delivery, parity, height, weight, smoking, marital status, and country of birth. Robust standard errors were used with clustering of births among siblings. Birth weight and length of the offspring were examined in separate models as alternatives to the standardized fetal growth variable. Maternal body mass index was examined in a separate model as an alternative to maternal height and weight. The reference category for all variables is indicated by an IRR of 1.00.